DETAILED ACTION

Acknowledgement of Receipt

Applicant's Response, filed 5/9/2011, in reply to the Office Action mailed 12/8/2010, is acknowledged and has been entered. Claims 1, 15, 18, 30 and 52 have been amended. Claims 2, 3, 7, 13, 16, 17, 21-29, 32, 33, 35-50 are cancelled. Claims 1, 4-6, 8-12, 14, 15, 18-20, 30, 31, 34 and 51-66 are pending, of which claims 18-20, 30, 31 and 34 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 1, 4-6, 8-12, 14, 15 and 51-66 are readable upon the elected invention and are examined herein on the merits for patentability.

Response to Arguments

Any rejection not reiterated herein has been withdrawn as being overcome by amendment.

Applicant's arguments have been fully considered but they are not persuasive for reasons set forth hereinbelow. In addition, new grounds for rejection are set forth herein necessitated by claim amendment.

Allowable Subject Matter

Claims 54-66 are allowable.

Claim Objections

Claims 10 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 5, 6, 8, 9, 11, 12 and 51–53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang *et al.* (*Applied Phys. Lett.*, 2003, 82(12), p. 1965-1967) in view of Weiss *et al.* (US 5,990,479).

Yang teaches CdS:Mn/ZnS core shell quantum dots that were prepared using a reverse micelle route. Surface passivation of a CdS:Mn core by a wider band gap material, ZnS led to suppressed nonradiative recombination and significantly enhanced luminescence intensity (page 1967, right column).

Yang does not specifically recite that the CdS:Mn/ZnS core shell quantum dots include an amine-functionalized silica coating and a targeting moiety.

Weiss teaches luminescent semiconductor nanocrystal compounds capable of linking to an affinity molecule to form an organo luminescent semiconductor nanocrystal probe capable of luminescence and/or absorption and/or scattering or diffracting when excited by an electromagnetic radiation source (of broad or narrow bandwidth) or a particle beam, and capable of exhibiting a detectable change in absorption and/or of emitting radiation in a narrow wavelength band and/or scattering or diffracting when so excited (column 1, lines 15-37). Treatment of a material with the organo luminescent semiconductor nanocrystal probe, and subsequent exposure of this treated material to excitation energy (from either a particle beam or an electromagnetic radiation source of broad or narrow bandwidth) to determine the presence of the detectable substance within the material, will excite the semiconductor nanocrystals in the organo luminescent semiconductor nanocrystal probe bonded to the detectable substance, resulting in the emission of electromagnetic radiation of a narrow wavelength band and/or a detectable change in the amount of energy being absorbed and/or scattered or diffracted, signifying the presence, in the material, of the detectable substance bonded to the organo luminescent semiconductor nanocrystal probe (column 1, lines 54+). The semiconductor nanocrystals useful in the practice of the invention include nanocrystals of Group II-VI semiconductors such as CdS, CdSe, CdTe, HgS, HgSe, HgTe, etc. In a preferred embodiment, the nanocrystals are used in a core/shell configuration wherein a first semiconductor nanocrystal forms a core ranging in diameter, for example, from

about 20 Å to about 100 Å, with a shell of another semiconductor nanocrystal material grown over the core nanocrystal to a thickness of, for example, 1-10 monolayers in thickness. When, for example, a 1-10 monolayer thick shell of CdS is epitaxially grown over a core of CdSe, there is a dramatic increase in the room temperature photoluminescence quantum yield (column column 5, line 60 – column 6, line 35). The particular affinity molecule forming a part of the organo-luminescent semiconductor nanocrystal probe of the invention will be selected based on its affinity for the particular detectable substance whose presence or absence, for example, in a biological material, is to be ascertained. Basically, the affinity molecule may comprise any molecule capable of being linked to a luminescent semiconductor nanocrystal compound which is also capable of specific recognition of a particular detectable substance. Such affinity molecules include, by way of example only, such classes of substances as monoclonal and polyclonal antibodies, nucleic acids (both monomeric and oligomeric), proteins, polysaccharides, and small molecules such as sugars, peptides, drugs, and ligands (column 6, lines 50+). There must be some type of linking agent present in the organo-luminescent semiconductor nanocrystal probe which is capable of forming a link to the inorganic semiconductor nanocrystal as well as to the organic affinity molecule in the organo-luminescent semiconductor nanocrystal probe. One form in which the semiconductor nanocrystal may be linked to an affinity molecule via a linking agent is by coating the semiconductor nanocrystal with a thin layer of glass, such as silica (SiO_x where x=1-2), using a linking agent such as a substituted silane, e.g., 3-mercaptopropyl-trimethoxy silane to link the nanocrystal to the glass. The glass-coated semiconductor

nanocrystal may then be further treated with a linking agent, e.g., an amine such as 3-aminopropyl-trimethoxysilane, which will function to link the glass-coated semiconductor nanocrystal to the affinity molecule. That is, the glass-coated semiconductor nanocrystal may then be linked to the affinity molecule (column 7-8). See also example 2.

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide a coating, such as an amine functionalized silica coating, on the CdS:Mn/ZnS core/shell quantum dot nanocrystals taught by Yang. One would have been motivated to do so because Weiss teaches that by coating semiconductor nanocrystals (i.e. preferably including core/shell structures) with such coatings and linking an affinity molecule thereto, the semiconductor nanocrystals are useable as a probe to determine the presence of a detectable substance in a material. One would have had a reasonable expectation of success in doing so because Weiss teaches CdS and ZnS as useable semiconductor materials, and also teaches the desirability of semiconductor nanocrystals capable of emitting light within a narrow wavelength band of about 40 nm or less, preferably about 20 nm or less, thus permitting the simultaneous use of a plurality of differently colored organo luminescent semiconductor nanocrystal probes with different semiconductor nanocrystals without overlap. The narrow emission bands of the CdS:Mn/ZnS quantum dots are well shown by Yang (e.g. Figure 3). It is noted that the affinity molecules recited by Weiss (antibody, protein, polysaccharide, nucleic acid, ligand, etc.) are within the scope of a targeting ligand, as claimed.

It is noted that the recitation of the intended use of the quantum dots as a contrast agent has not been given patentable weight to distinguish over Yang because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Yang discloses compounds meeting the structural requirements of the instant claims, they would be capable of performing the intended use, as claimed.

It is further noted that Yang does not specifically recite that the quantum dot is fluorescent, radio-opaque and paramagnetic. However, when a structure recited in a reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent, see MPEP 2112.01. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). It is further noted that the specification at published paragraph 0091-0092 states that highly water-dispersible, multifunctional CdS:Mn/ZnS core-shell Qdots prepared using microemulsion methods are fluorescent, radio-opaque and paramagnetic, and that the Qdots were synthesized following Yang's procedure (*Appl. Phys. Lett*, 2003, 82, p. 1965-1967).

Regarding claim 51, the quantum dots may in solution may be "implanted" or "deployed." Regarding claims 52-53, the quantum dots are present within aqueous reverse micelle solution, which is within the scope of a carrier. Water or surfactants within the solution are considered to be within the scope of pharmaceutically active agents.

Response to Arguments

Applicant argues on pages 7-9 of the Response that the Yang reference is cited for the teachings set forth in the 102 rejection and that the Weiss patent is cited as teaching luminescent semiconductor nanocrystal compounds capable of linking to an affinity molecule to form an organo luminescdent semiconductor nanocrystal probe capable of luminescence and/or absorption and/or scattering or diffracting when excited by an electromagnetic radiation source or a particle beam, and capable of exhibiting a detectable change in absorption and/or of emitting radiation in a narrow wavelength band and/or scattering or diffracting when so excited. Applicant asserts that the cited reference s do not teach or suggest the claimed invention. Applicant submits that the CdS:Mn/ZnS quantum dots of the present invention are multimodal (e.g. fluorescent and paramagnetic), and that the application distinguishes over the cited art in several aspects (i) it teaches Qdots having multimodality, (ii) it teaches improvement of the paramagnetic property by further surface modification with Gd-chelates, and (iii) it provides for co-existence of two paramagnetic centers within the same nanoparticle (paramagnetic Mn in core and paramagnetic Gd chelated to silica shell).

This is not found to be persuasive. With regard to (i) above, the CdS:Mn/ZnS core/shell quantum dot nanocrystals taught by Yang would inherently have the properties of being luminescent and paramagnetic, as set forth in the previous Office Action. Products of identical chemical composition cannot have mutually exclusive properties. With regard to (ii) and (iii) above, it is noted that these arguments are not commensurate in scope with the subject matter which is claimed. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., Gd chelated to silica shell) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Claims 1, 4-6, 8, 9, 11, 12 and 51–53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang *et al.* (*Applied Phys. Lett.*, 2003, 82(12), p. 1965-1967) in view of Weiss *et al.* (US 5,990,479), in further view of Prober *et al.* (US 2005/0019842).

The rejection over Yang in view of Weiss is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the invention to provide folic acid as an affinity molecule in the probes of Weiss when the teachings of Yang and Weiss are taken in view of Prober.

Prober teaches microparticle-based analysis in biological and chemical assays (abstract). Detectable labels in the probes include quantum dots (paragraph 0159; claim 8). Probe/target binding pairs, in which either member of the pair may be the

probe and the other the analyte; antigen and specific antibody, folic acid and folate binding protein, nucleotide and complementary nucleotide, etc. (paragraph 0242).

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ folic acid as a functionally equivalent affinity molecule on an organo luminescent semiconductor nanocrystal probe to those taught by Weiss. Weiss teaches that basically, the affinity molecule may comprise any molecule capable of being linked to a luminescent semiconductor nanocrystal compound which is also capable of specific recognition of a particular detectable substance. Such affinity molecules include, by way of example only, such classes of substances as monoclonal and polyclonal antibodies, nucleic acids (both monomeric and oligomeric), proteins, polysaccharides, and small molecules such as sugars, peptides, drugs, and ligands (column 6, lines 50+). Prober teaches that probe/target binding pairs include folic acid/folate binding protein, in addition to antibody and nucleotide. One of ordinary skill in the art could have readily employed folic acid as a functionally equivalent affinity molecule as antibody, nucleotide, etc. and the result would have been predictable, that is providing a luminescent semiconductor nanocrystal probe having an affinity molecule attached thereto.

Claims 1, 5, 6, 8, 9, 11, 12, 14 and 51–53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang *et al.* (*Applied Phys. Lett.*, 2003, 82(12), p. 1965-1967) in view of Weiss *et al.* (US 5,990,479), in further view of Svarovsky (US 2008/0039816).

The rejection over Yang in view of Weiss is applied as above. It would have been further obvious to one of ordinary skill in the art at the time of the invention to provide a carbohydrate such as galactose as an affinity molecule in the probes of Weiss when the teachings of Yang and Weiss are taken in view of Svarovsky.

Svarovsky teaches that quantum dots are small semiconductor particles that exhibit quantum confinement. Quantum dots can be made to luminesce at their characteristic wavelength by exposing them to light having a wavelength shorter than the characteristic wavelength. The essential part of the quantum dot is a nanocrystalline core (paragraphs 0002-0004). To increase the quantum efficiency of a nanocrystalline core, and thereby enhance the intensity of luminescence, the nanocrystalline core can be overcoated with a shell layer of a semiconductor material which has a band gap greater than the band gap of the nanocrystalline core. A quantum dot having both a nanocrystalline core and a shell layer can be referred to as a core/shell quantum dot (paragraph 0006). Chemical groups, including groups which have an effect on a biological system, can be bound to the surface of a nanocrystalline core or a shell of a quantum dot, which makes them of great interest in the development of new materials and techniques for biological research and medical diagnosis (paragraph 0007). Coupling of receptors to cell-surface saccharides mediates many relevant biological processes, including differentiation, motility, adhesion, tumor progression and metastasis. Therefore, quantum dots functionalized with saccharides are of interest for biological research, medical diagnostic and therapeutic applications (paragraph 0016). The invention provides novel biofunctionalized quantum dots which

luminesce brightly, are hydrophilic, and are stable in aqueous solution, and provides quantum dots which have saccharides linked to the surface of a nanocrystalline core or shell (paragraph 0019). The biofunctional group on a quantum dot can be a saccharide, for example a tumor associated carbohydrate; a Thomsen-Friedenreich (T_f) disaccharide (paragraph 0021). The quantum dot can be dissolved or suspended in a liquid (paragraph 0024) or can be linked to the surface of a device to form a coating on the device (paragraph 0027). Examples of core materials include cadmium sulfide, etc., and can also be doped with one or more suitable dopants (paragraph 0080). A shell layer overcoating and surrounding a nanocrystalline core may be present, including zinc sulfide, etc (paragraph 0081). See figures and examples for galactose containing saccharides conjugated to CdSe/ZnS quantum dots, as well as galactose-peg-HgTe.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ a carbohydrate such as galactose as a functionally equivalent affinity molecule on an organo luminescent semiconductor nanocrystal probe to those taught by Weiss. Weiss teaches that basically, the affinity molecule may comprise any molecule capable of being linked to a luminescent semiconductor nanocrystal compound which is also capable of specific recognition of a particular detectable substance. Such affinity molecules include, by way of example only, such classes of substances as polysaccharides and small molecules such as sugars, etc. (column 6, lines 50+). While Weiss does not specifically recite galactose as sugar, it is known in the art to provide galactose as a coating on quantum dot as shown by Svarovsky. One would have been motivated to do so because Svarovsky teaches that quantum dots

functionalized with saccharides are of interest for biological research, medical diagnostic and therapeutic applications (paragraph 0016) and that luminescent biofunctionalized quantum dots can therefore be imaged in a method of medical imaging, such as luminescing quantum dots adhered to a secretion of biological material can be imaged (e.g. cell culture or in vivo) (paragraph 0025). One would have had a reasonable expectation of success in doing so because Svarovsky teaches that the core of the quantum dot to be biofunctionalized can include CdS, including doped nanocrystals, and that suitable shell materials include ZnS.

Conclusion

Claims 1, 4-6, 8, 9, 11, 12, 14 and 51-53 are rejected. Claims 10 and 15 are objected to. Claims 54-66 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is (571)272-9928. The examiner can normally be reached on Monday-Wednesday 9 AM-5 PM and telework Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LHS/

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